Emotional Content Enhances Effective Connectivity in the Visual Neural Network - an fMRI Study

Antti Johannes Nuortimo
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Supervisors: Laura Hokkanen
Tage Orenius

HELSINGIN YLIOPISTO – HELSINGFORS UNIVERSITET – UNIVERSITY OF HELSINKI

Tiedekunta – Fakultet – Faculty	Laitos – Institution – Department
Faculty of Behavioural Sciences	Institute of Behavioural Sciences

Tekijä – Författare – Author

Antti Johannes Nuortimo

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Tiivistelmä – Abstrakt – Abstract

Aims. Understanding of emotional processing is important for the research of mental states. A better understanding of the visual system would facilitate understanding the functioning of the entire brain. Emotions are processed in a complex neural network. The aim of the present Master's thesis is to explore the effective connectivity of the occipital face areas (OFAs) and fusiform face areas (FFAs) during the processing of visual stimuli eliciting negative emotion.

Methods. The subjects (n = 16) were young adult male students. Negative and neutral emotion were elicited using visual stimuli from the International Affective Picture System (IAPS). Functional magnetic resonance imaging (fMRI) data were acquired using an MRI scanner. The fMRI data were preprocessed and analyzed using SPM8 software. In order to proceed to the psycho-physiological interaction (PPI) analyses, imaging sessions were concatenated and entered into the analyses as one single session. Subject-level model comprised the following regressors: negative emotion, neutral emotion, baseline and a binary regressor for each functional session to model session effects. An effects of interest F-contrast and a negative emotion t-contrast were defined. Spherical volumes of interest (VOIs) were computed for each subject for the left and the right occipital face area (OFA) and for the left and the right fusiform face area (FFA). The PPI variables were computed for each statistically significant VOI. A standard PPI model was defined. Each of the 4 VOIs was used as source region for all other VOIs. A group-level whole brain analysis was done for each PPI source VOI. Group-level VOI analyses were conducted for all PPI source VOIs.

Results and conclusions. In the whole brain analyses statistically significant group-level PPIs were found in the following brain regions: left cuneus, right middle occipital gyrus, right and left inferior occipital gyrus, left lingual gyrus, and the left culmen. VOI analyses demonstrated the strong connectivity in the network consisting of the right OFA and left and right FFAs. Negative emotional content enhances effective connectivity in the bilateral OFA-FFA network.

Avainsanat – Nyckelord – Keywords

emotion, functional magnetic resonance imaging, neural connectivity, visual cortex

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Emotionaalinen sisältö vahvistaa seurannaisyhteyksiä visuaalisessa hermoverkossa - toiminnallinen magneettikuvaustutkimus

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Tiivistelmä – Abstrakt – Abstract

Tavoitteet. Tunteiden prosessoinnin ymmärtäminen on tärkeää psyykkisten tilojen tutkimuksen kannalta. Näköjärjestelmän parempi ymmärrys auttaisi koko aivojen toiminnan ymmärtämisessä. Tunteita prosessoidaan monimutkaisessa hermoverkossa. Tämän pro gradun tavoitteena on tutkia takaraivolohkon kasvoja prosessoivien alueiden (occipital face area, OFA) ja ohimolohkon gyrus fusiformiksen kasvoja prosessoivien alueiden (fusiform face area, FFA) välisiä seurannaisyhteyksiä (ns. efektiivistä konnektiviteettia) negatiivista emootiota tuottavien visuaalisten ärsykkeiden prosessoinnin aikana.

Menetelmät. Koehenkilöt (n = 16) olivat nuoria aikuisia miesopiskelijoita. Negatiivista ja neutraalia emootiota tuotettiin käyttäen visuaalisia ärsykkeitä International Affective Picture System (IAPS) -kuvasarjasta. Aivot kuvattiin magneettikuvauslaitteella. Toiminnallinen magneettikuvausdata esikäsiteltiin ja analysoitiin SPM8-ohjelmistolla. Psykofysiologisia interaktioanalyyseja (PPI) varten kuvasarjat liitettiin yhteen ja syötettiin analyyseihin yhtenä kuvasarjana. Koehenkilötason malli sisälsi seuraavat regressorit: negatiivinen emootio, neutraali emootio, vertailutaso ja binäärinen regressori kullekin kuvasarjalle kuvasarjakohtaisten vaikutusten mallintamiseksi. Kiinnostuksen kohteena olevien efektien F-kontrasti ja negatiivisen emootion t-kontrasti määriteltiin. Pallonmuotoiset kohdetilavuudet (VOI) laskettiin kullekin koehenkilölle vasemmalle ja oikealle OFA:lle ja FFA:lle. PPI-muuttujat laskettiin kullekin tilastollisesti merkitsevälle VOI:lle. Tavanomainen PPI-malli määriteltiin. Kutakin neljästä VOI:sta käytettiin lähdealueena kaikille muille VOI:lle. Ryhmätason kokoaivoanalyysi tehtiin jokaiselle PPI-lähde-VOI:lle. Ryhmätason VOI-analyysit tehtiin jokaiselle PPI-lähde-VOI:lle.

Tulokset ja johtopäätökset. Kokoaivoanalyyseissä tilastollisesti merkitseviä ryhmätason PPI:tä löytyi seuraavilta aivoalueilta: vasen cuneus, oikea keskimmäinen gyrus okkipitalis, oikea ja vasen alempi gyrus okkipitalis, vasen gyrus lingualis ja vasen culmen. VOI-analyysit osoittavat voimakkaita seurannaisyhteyksiä oikeasta OFA:sta ja vasemmasta ja oikeasta FFA:sta koostuvassa hermoverkossa. Negatiivinen emotionaalinen sisältö vahvistaa seurannaisyhteyksiä bilateraalisessa OFA-FFA-hermoverkossa.

Avainsanat – Nyckelord – Keywords

emootio, toiminnallinen magneettikuvaus, neuraalinen konnektiviteetti, näköaivokuori

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Contents

Forewords

The Master's thesis is a part of a larger functional magnetic resonance imaging (fMRI) study of pain-emotion interaction by a research group comprising: Tage Orenius, PsL, Chief psychologist; Tuukka Raij, MD, PhD, Psychiatrist; Petri Näätänen, PsL, Chief of development; Jari Lipsanen, PsM, University lecturer; Hasse Karlsson, MD, PhD, Professor in Psychiatry and integrative neuroscience; Antti Nuortimo, psychology student, research assistant. The investigation was conducted in Advanced Magnetic Imaging (AMI) Centre, at Aalto University, Espoo, Finland.

Several people have helped me in the process of the present Master's thesis, I thank them all for their help. I thank Tage Orenius for supervision and for the chance to make my Master's thesis in connection with his research project. I also thank Prof. Laura Hokkanen for the supervision. I thank Tuukka Raij for teaching me the usage of SPM8 and providing excellent answers to my fMRI-related questions. Tapani Riekki provided essential technical assistance. The help given by Sebastian Cederström was crucial in my very first steps of MATLAB programming. Jari Lipsanen provided expert advice on statistical methods. The feedback from Mari Tervaniemi and Noora Ovaska helped me a lot. Noora Ovaska and Johanna Jutila proofread the final draft. With Aki Kuitunen I had inspiring conversations. Adriana Paredes Cruz and Anu Lähde provided important moral support throughout the project. Finally, I would like to thank all my friends and family who have supported me during this long journey and with whom I have had many interesting discussions on the topic.

Principal Acronyms

BA Brodmann area

DCM dynamic causal modeling (fMRI analysis method)

EPI echo-planar imaging (fMRI sequence type)

FG fusiform gyrus

FFA fusiform face area

fMRI functional magnetic resonance imaging

IAPS International Affective Picture System

IFC inferior frontal cortex

IOG inferior occipital gyrus

ITC inferotemporal cortex

LG lingual gyrus

mPFC medial prefrontal cortex

MRI magnetic resonance imaging

OFA occipital face area

OFC orbitofrontal cortex

PPI psychophysiological interaction (fMRI analysis method)

SPM statistical parametric mapping (fMRI analysis method), also neuroimaging software called SPM

STS superior temporal sulcus

vmPFC ventromedial prefrontal cortex

1 Introduction

Given the paramount importance of emotional processing for humans, a species adapted to complex social environments, broader understanding of emotional processing is very important for the research of mental states. The neural circuitry executing the processing of visual stimuli in general is not thoroughly understood in detail (DiCarlo, Zoccolan, & Rust, 2012). The visual neural network is currently the best studied of all neural networks and a better understanding of the visual system would probably be beneficial as a model system for understanding the functioning of the entire brain (Revonsuo, 2006). Visual cortex occupies approximately 23 percent of the human cortex (Van Essen & Drury, 1997).

1.1 Emotions and Emotional Content

Emotions are episodes of synchronous or simultaneous changes in physiological arousal, motor expression and subjective feeling (Péron & Grandjean, 2014). Basic emotions are fear, anger, joy and sadness (Salas, Radovic, & Turnbull, 2012).

Emotional content refers to those aspects of the stimuli that cause or trigger emotions. Emotion can be induced by visual, auditive, tactile, or olfactory stimuli. In the majority of functional magnetic resonance imaging (fMRI) studies on emotion processing, either emotional faces or emotional scenes have been used as visual stimuli (Sabatinelli et al., 2011). A widely used emotional scene image databank is the International Affective Picture System (IAPS), a series of standardized images (Lang, Bradley, & Cuthbert, 2005). Facial images and complex real-life images activate a similar network, consisting of amygdala, posterior hippocampus, ventromedial prefrontal cortex (vmPFC) and visual cortex (Britton, Phan, et al., 2006). Presumably these regions also play a major part in the general neural processing of emotional visual stimuli. Recent research shows that emotions are beneficial for social interaction by syncronizing brain activity across individuals (Nummenmaa et al., 2012), enabling simulation of others' emotional states and prediction of their intentions and actions.

1.2 Neural Connectivity

Neural connectivity is a broad research field comprising anatomical connectivity and functional integration. In anatomical connectivity neuroimaging methods based on some structural data of the brain are used. Functional integration refers to the functional neuroimaging analysis methods which investigate the extrinsic connections between brain regions. Functional integration can be measured using two approaches: functional connectivity and effective connectivity (Stephan & Friston, 2010). The importance of functional integration lies on the fact that the different activation levels in different subregions of the brain can neither adequately explain brain functions for any given task (Cohen, 2011) nor reveal the functional principles of the architecture of the brain (K. Friston, 2002).

Functional connectivity analysis comprises methods (eg. Granger causality; Granger, 1969) using functional neuroimaging data (usually fMRI) explaining the changes in neuronal activity in the brain without an a-priori defined model or neural network. In effective connectivity methods, an a-priori defined model or neural network is used and effective connectivity is defined as the influence one neural system exerts on another (Büchel & Friston, 1997). Examples of effective connectivity analysis methods include psychophysiological interaction (PPI; K. J. Friston et al., 1997) and dynamic causal modeling (DCM; K. J. Friston, Harrison, & Penny, 2003). PPI is a functional neuroimaging analysis method which enables inferences about the effective connectivity of the brain and is based on extensions to statistical models of factorial designs (K. J. Friston et al., 1997). In PPI the blood oxygen level dependent (BOLD) response of each voxel is modeled in terms of interaction between the BOLD response of the source region and a psychological factor (K. J. Friston et al., 1997).

1.3 Neural Networks Linked to the Processing of Emotional Content

Functional neuroimaging studies on emotional processing aim to explain the functional localization and functional integration of the neural networks participating in emotional processing. For a review of the localization studies on emotional processing, see Fusar-Poli et al. (2009).

1.3.1 Functional Localization of Emotional Processing

Functional localization method is the foundation of contemporary neuroimaging. Although it does not provide information about functional integration, it is relevant for the purposes of the present Master's thesis in defining brain regions to be included in PPI. Functional localization studies usually apply the statistical parametric mapping (SPM) analysis method, unless otherwise specified.

According to Pessoa and Adolphs (2010) the emotional valence is probably processed in several different brain regions, including the orbitofrontal cortex (OFC). They discuss the issue of relative latencies of different brain regions participating in visual processing and conclude that latencies of 'late' visual areas such as the inferotemporal cortex (ITC) are as short as 60-85 ms. The amygdala responses in monkeys have been in turn detected within the 100-200 ms latence range. The amygdala receives multiple connections with cortical and subcortical sites, which provide highly processed sensory information from all sensory modalities except the olfaction. This suggests that the role of the amygdala is to function as a convergence zone for sensory data. Finally, they conclude that visual information is processed in a complex network, in which each processing stage adds approximately 10 ms to the latency (Pessoa & Adolphs, 2010). However, models applying hierarchical structure of visual processing brain regions still have not reached a good fit for existing latency data (Capalbo, Postma, & Goebel, 2008; Pessoa & Adolphs, 2010), suggesting shortcut connections (Pessoa & Adolphs, 2010). The fusiform face area (FFA) located in the fusiform gyrus (FG) within the Brodmann area (BA) 37 is a specialized brain region that processes mostly different aspects of facial recognition (Brassen, Gamer, Rose, & Büchel, 2010; Fairhall & Ishai, 2007; Rossion, Schiltz, & Crommelinck, 2003). The occipital face area (OFA; BA 19; Rossion, Schiltz, & Crommelinck, 2003) is also implicated to be specialized in face processing (Gauthier et al., 2000; Rossion, Schiltz, & Crommelinck, 2003) and its activation commonly co-occurs with FFA activation (Gauthier et al., 2000). The FFA-OFA network shows right hemisphere dominance (Minnebusch, Suchan, Köster, & Daum, 2009; Rossion, Caldara, et al., 2003). However, both FFA and OFA have been considered as domain-general regions specialized in identifying the specific identity of the stimuli within a category (Haist, Lee, & Stiles, 2010), and both FFA and OFA show similar bilateral response to faces, diverse objects and watches (Haist et al., 2010). Evidence from a study with patients suffering from a vi-

suospatial hemineglect deficit supports the assumption of modulatory top-down connections for visual emotional stimuli (Grabowska et al., 2011).

Studies following the static emotional face paradigm and studies using complex real-life images of emotional situations have revealed neural activations in partly different brain regions (Britton, Taylor, Sudheimer, & Liberzon, 2006). According to a recent meta-analysis by Sabatinelli et al (2011), the localized activations of emotional faces and emotional scenes partly overlap, especially in the amygdala, but also in the medial prefrontal cortex (mPFC), the inferior frontal cortex (IFC), the ITC and the extrastriate occipital cortex. Either class of these stimuli constantly activates brain regions specific to the stimulus type (Sabatinelli et al., 2011).

1.3.2 Functional Integration of Emotional Processing

In their review, Haxby, Hoffman and Gobbini (2000) present a model of distributed neural system for face perception. According to this model, facial emotion is processed within an extended system, specifically in a network comprising the amygdala, the insula and the limbic system. This network is reciprocally connected with the superior temporal sulcus (STS; Haxby et al., 2000). In a further revised model, the same network is reciprocally also connected with the lateral FG and the anterior temporal region (Haxby, Hoffman, & Gobbini, 2002).

From an evolutionary point of view, negative emotion may be a signal of a potential danger. Fearful facial expressions have been shown to increase gaze-cueing in both adults and children (Dawel, Palermo, O'Kearney, Irons, & McKone, 2014). The vmPFC shows increased electroencephalography (EEG) response to subjectively unconscious negative visual stimuli 150 ms after stimulus onset, and 500 ms after stimulus onset the vmPFC and visual association cortices increase activation simultaneously (Carretié, Hinojosa, Mercado, & Tapia, 2005). This top-down regulation from the vmPFC to visual association cortices is likely to be completely automatic and unconscius and it facilitates danger processing (Carretié et al., 2005). The synchronized activity in the bilateral inferior occipital gyrus (IOG)-FG network in response to negative images is probably caused by top-down regulation from the vmPFC, though some other regions may also be involved.

In a DCM study by Fairhall and Ishai (2007) on effective connectivity of face perception

it was found that between different models consisting of the IOG, the FG and the STS as nodes of the network, the most probable one was a model in which both FG and STS receive direct input from the IOG with no reciprocal or lateral connections. Moreover, they found that emotional faces significantly increased the influence of the IOG on the FG. Further, using an extended model, they found that viewing emotional faces caused a significant increase in the effective connectivity between each link of the IOG-FG-amygdala pathway (Fairhall & Ishai, 2007).

Ishai (2008) proposes a reciprocally connected face perception network consisting of the IOG, the FG, the STS, the amygdala, the inferior frontal gyrus, and the orbitofrontal cortex, in which viewing emotional faces increases effective connectivity between the FG and the amygdala (Ishai, 2008). In a PPI study with a threat - non threat comparison (Satterthwaite et al., 2011) bilateral amygdala exerted significant influence on several other brain regions: left parahippocampal gyrus, right temporal pole, bilateral FG, bilateral lateral occipital cortex, bilateral subcallosal cingulate cortex and left insula.

1.4 The Aim of the Study

Literature shows that emotional states are processed in a complex neural network of several brain areas. A better understanding of the neural processing of emotions is important for the research of mental states. The aim of this Master's thesis is to explore the effective inter- and intrahemispheric connectivity of the OFAs and the FFAs during the processing of visual stimuli eliciting negative emotion.

The hypotheses are:

1. Negative emotion increases the interhemispheric effective connectivity of the OFA.
2. Negative emotion increases the interhemispheric effective connectivity of the FFA.
3. Negative emotion increases the bottom-up effective connectivity between left OFA and left FFA.
4. Negative emotion increases the bottom-up effective connectivity between right OFA and right FFA.

2 Methods

2.1 Subject Selection

The study subjects were 16 healthy young adult male engineering students, selected from a sample of 249 at Helsinki Metropolia University of Applied Sciences. Male subjects were selected to increase homogeneity in emotional processing. Two subjects were discarded based on their fMRI data: one subject had excessive ($> 2^{\circ}$) head rotation in all echo-planar imaging (EPI) sessions, and other subject did not have expected visual cortex activation in visual $>$ baseline contrast, indicating that the subject did not attend to the stimuli. The data of the 14 remaining subjects were analyzed.

Exclusion criteria were depression and alexithymia, defined as a cognitive deficit in the regulation of emotions (G. J. Taylor, Parker, Bagby, & Acklin, 1992). A Finnish version of the 21-item Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 2004), was used to screen for depressive symptoms. The BDI-II exclusion cutoff score was ≥ 14, which is the reference value for mild depression (Beck et al., 2004). No participant exceeded the reference cutoff score for mild depression. The Finnish version of the Toronto Alexithymia Scale (TAS-20) was used to screen for alexithymia (Joukamaa et al., 2001). Reference cutoff score for alexithymia is > 60 (G. J. Taylor et al., 1992). No participant exceeded the reference cutoff score for alexithymia.

Other exclusion criteria were: earlier or present prolonged pain, psychiatric diagnosis, regular medication of any kind, and ferromagnetic objects in the body. All subjects filled in a safety questionnaire including the exclusion criteria before entering the magnetic resonance imaging (MRI) device.

2.2 Stimulus Delivery

2.2.1 IAPS Pictures

Negative and neutral emotion were elicited using visual stimuli from the standardized IAPS (Lang et al., 2005; Meagher, Arnau, & Rhudy, 2001), which consists of a series of emotional, normative and internationally accessible pictorial stimuli and is considered to be the most reliable and valid system in the experimental study of emotions. It is frequently used as an

Table 1: List of IAPS Images with Negative and Neutral Valences in the Order of Presentation in Each Echo-Planar Imaging (EPI) Session

valence	mean	SD	IAPS image numbers						
negative	2.78	0.39	session 1:	9265,	3005.1,	2455,	9430,	9423,	9910,	6838
			session 2:	2750,	3300,	9432,	2205,	9050,	9419,	2900
			session 3:	2276,	2141,	9921,	2095,	2799,	3301,	2661
neutral	5.02	0.34	session 1:	2383,	2780,	2357,	2870,	2690,	2191,	2980
			session 2:	2410,	2280,	2512,	2516,	2210,	2270,	2445
			session 3:	2394,	2493,	2385,	2495,	9913,	2441,	2214

Note. SD = standard deviation.

independent variable in neuroimaging studies (Jayaro, de la Vega, Díaz-Marsá, Montes, & Carrasco, 2008). The images were presented in a pseudorandom order, each EPI session consisting of the same number of negative and neutral IAPS images. Stimuli were presented for a time period of 6 seconds each. The IAPS image numbers are presented in table 1.

2.2.2 The MRI Procedure

All MRI data were acquired using the GE Signa VH/i 3.0 T MRI scanner (General Electrics, Milwaukee, WI, USA) at the Advanced Magnetic Imaging (AMI) Centre, at Aalto University, Espoo, Finland.

For each imaging session, BOLD signal was acquired using a full-head gradient-echo, EPI sequence, with the following parameters: time to repetition = 2000 ms, time to echo/time to inversion = 32 ms, flip angle = 75°, oblique plane, 64×64 acquisition matrix, number of excitations = 1, field of view = 22 cm, slice thickness = 4.0 mm, voxel size $3.44 \times 3.44 \times 4$ mm, no spacing, number of slices = 34, frequency direction = right/left (R/L), interleaved slice order from down to up, 450 time points, 4 dummies.

2.3 Processing of Neural Data

The neural data were analyzed using Statistical Parametric Mapping 8 software (SPM8) revision 4667 (`http://www.fil.ion.ucl.ac.uk/spm/`) and MATLAB R2012b (8.0.0.783). FSLVIEW (`http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL/`; Smith et al., 2004) was used for checking the slice numbering order and the precise voxel size of the fMRI data

Table 2: Conditions Used in the Model

condition	duration of each block
negative images	3 volumes (6 s)
neutral images	3 volumes (6 s)
baseline	5-7 volumes (10-14 s)
session 1 (0/1)	length of session 1 (408 volumes)
session 2 (0/1)	length of session 2 (423 volumes)
session 3 (0/1)	length of session 3 (421 volumes)

and also for visually checking the results of the preprocessing. xjView 8.11 (`http://www.alivelearn.net/xjview/`) was used for checking the brain regions of the whole brain results.

The Digital Imaging and Communications in Medicine (DICOM) format MRI images were first converted into the Neuroimaging Informatics Technology Initiative (NIfTI) format used in SPM8. Each EPI session was separately realigned to the mean image of the EPI session, using 7th degree B-spline interpolation to avoid realigning artifacts (Rohde, Aldroubi, & Healy, 2009), standard 5 mm full width at half maximum (FWHM) smoothing kernel, and 1 mm separation distance. After realigning the fMRI data were spatially normalized using 7th degree B-spline interpolation. Finally, the fMRI volumes were spatially smoothed with an isotropic Gaussian filter (8 mm FWHM) to compensate for intersubject anatomical and functional variability.

2.4 Analyses of Neural Data

In order to proceed to the PPI analyses, functional sessions were concatenated and entered into the analyses as one single session. Subject-level model comprised the following regressors or conditions: negative emotion, neutral emotion, baseline and a separate binary (0/1) regressor for each functional session to model session effects. See table 2 for details. The first 4 volumes and all volumes after the last stimulus were discarded from each EPI session. Subject head movement was modeled using six realignment parameters (pitch, roll, yaw, translation x, translation y, translation z) as parametric regressors. The model was estimated using classical inference. The following contrasts were defined: an effects of interest F-contrast (I_2, a 2 x 2 identity matrix) and a negative emotion t-contrast, with contrast

Table 3: A Priori Defined MNI Coordinates for Volumes of Interest (VOI)

brain region	Talairach coordinates	MNI coordinates	radius
left OFA	(-33.60, -81.00, -14.40)	(-34, -83, -22)	10 mm
right OFA	(37.67, -80.44, -7.33)	(38, -82, -14)	10 mm
left FFA	(-35.62, -52.88, -15.12)	(-36, -54, -21)	10 mm
right FFA	(41.36, -50.36, -16.18)	(42, -51, -22)	10 mm

Note. MNI = Montreal Neurological Institute; OFA = occipital face area; FFA = fusiform face area. Talairach coordinates are mean coordinates from Rossion, Caldara, et al. (2003), which were converted to MNI coordinates using Brett algorithm (implemented in tal2mni.m function of SPM8) and rounded to the nearest whole mm.

weight +1 for negative emotion regressor, -1 for neutral emotion regressor, and 0 for the rest regressors.

A priori defined spherical volumes of interest (VOIs) were computed for each subject, for negative emotion contrast, and adjusted for effects of interest F-contrast for each of the following brain regions: left OFA, right OFA, left FFA, and right FFA. See table 3. All VOI coordinates were taken from an earlier study (Rossion, Caldara, et al., 2003). Family-wise error (FWE) correction at rate $p < .05$ was used to avoid type I errors (false positive findings). Cluster threshold 0 voxels and a radius of 10 mm were used for all VOIs.

The PPI variables were computed for each statistically significant VOI. Statistically non-significant ($p < .05$) VOIs were discarded separately for each subject. From the total of 56 potential VOIs (14 subjects x 4 source VOIs), 35 were statistically significant and were selected for further analysis. A PPI variable was computed for each VOI, using a negative emotion $>$ neutral emotion contrast.

For the PPI analyses a standard PPI model was defined with the following regressors: the PPI interaction term, the eigenvariate of BOLD signal of the source VOI (a covariate of no interest), and the main effect of emotion. For each EPI session, a binary regressor (comprising ones for the volumes of a specific session and zeros for all other volumes) was created to account for between-session variability. A PPI interaction contrast was defined so that the weight of the PPI interaction term was set to 1 and the weights of other regressors were set to 0. This was repeated for each subject and for each PPI source VOI (left OFA, right OFA, left FFA, right FFA).

The analysis parameters were specified and estimated and the results of each contrast

were computed for each subject running SPM8 in batch mode using a custom MATLAB program (ultraSPM version 0.0.1). The t-values were scaled according to the number of subject's EPI sessions after the exclusion of EPI sessions in which head movement exceeded the 4 mm limit and/or rotation exceeded the 2° limit.

To investigate the effective connectivity of the bilateral OFA-FFA network, each of the 4 defined VOIs was used as a source region and each VOI was also used as a target region for all other VOIs.

2.4.1 Whole Brain Analyses of Psychophysiological Interaction (PPI)

After the subject-level PPI analyses, the contrast images were entered into the group-level analyses. A separate group-level analysis was done for each PPI source VOI. As some subjects' VOI analyses were discarded, different group-level analyses have PPI source VOIs from different subjects and the number of subjects varies between different PPI source VOIs. A contrast was defined as follows: in negative emotion contrast the weight of PPI interaction was set to 1 and the weights of other regressors were set to 0. A $p_{FWE} < .05$ limit and cluster threshold 0 voxels were used.

2.4.2 Volume of Interest (VOI) Analyses of Psychophysiological Interaction (PPI)

After group-level whole-brain analyses, group-level VOI analyses were conducted using each PPI source VOI as a target VOI for all other PPI source VOIs. All statistical parametric maps (SPMs) were estimated using frequentist inference and the general linear model approach.

2.5 Ethics and Safety

The study was approved by the Ethics Committee for Psychiatry and Pediatrics at the Helsinki and Uusimaa Hospital District (permission No: 109/E7/2005) as well as the scientific board at ORTON Ltd., ORTON Foundation (permission No: 327). The participants read and filled in the MRI safety questionnaire and were scanned with a metal detector before entering the MRI scanner. Verbal and written information about the study was given to each subject before signing an informed consent form; each subject signed the form before attending the

study.

3 Results

3.1 Whole Brain Analyses of Psychophysiological Interaction (PPI)

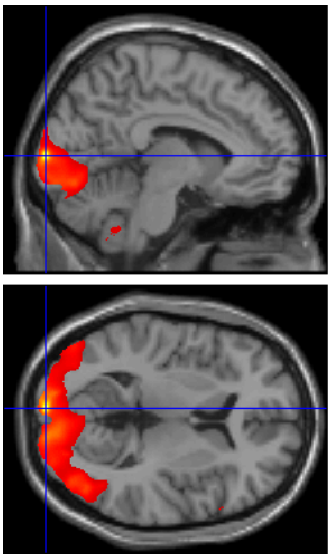
Statistically significant ($p_{FWE} < .05$ used for each source VOI) group-level PPIs were found for the negative emotion contrast and for the left FFA as source VOI in the following regions: left cuneus, right middle occipital gyrus (MOG), right IOG, right BA18/MOG, and left lingual gyrus (LG). For the right FFA, statistically significant PPIs were found in the right IOG, the left culmen, and the left IOG. For the left and right OFA no statistically significant PPIs were found in the whole brain analyses.

Table 4 shows PPI whole brain results for the negative emotion contrast. Figures 1, 2, and 3 show the overall activation for the negative emotion contrast.

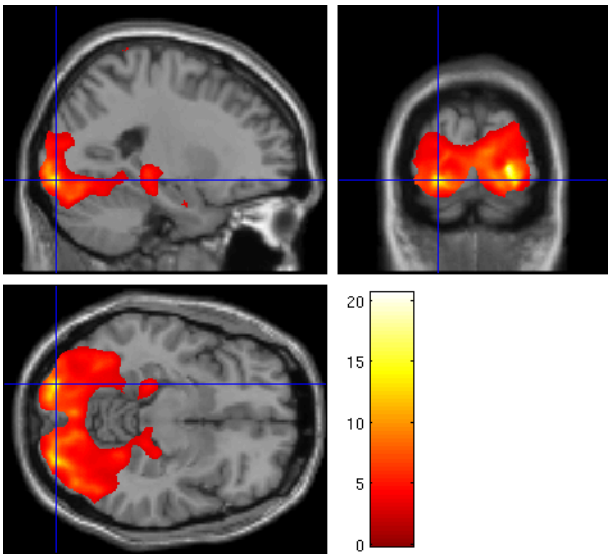
3.2 Volume of Interest (VOI) Analyses of Psychophysiological Interaction (PPI)

Several statistically significant group-level PPIs were found in the network between the chosen brain regions.

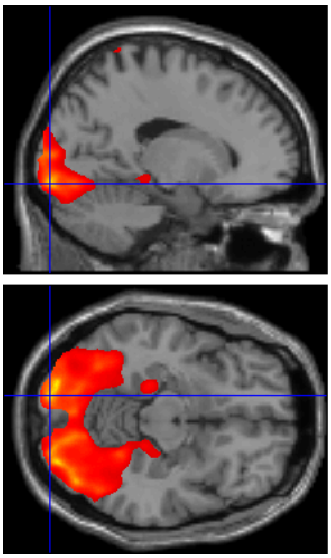
Tables 5, 6, 7, and 8 show PPI VOI results for the negative emotion contrast. Figure 4 shows the VOI analyses of PPI for each source VOI. Figure 5 shows the network based on the statistically significant PPI effective connectivity between the regions of the OFA-FFA network.



(a) Global maximum at -7, -98, 7.

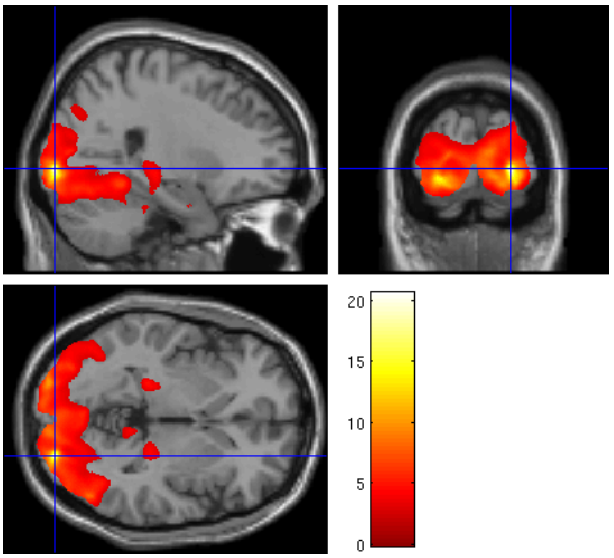


(b) Local maximum at -23, -91, -10.

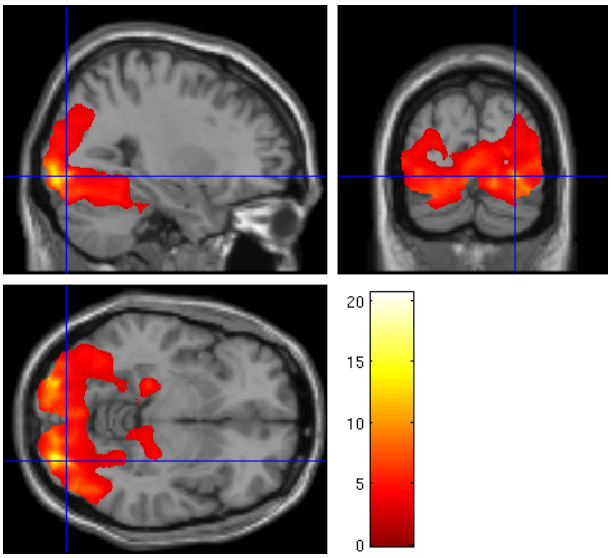


(c) Local maximum at -16, -95, -12.

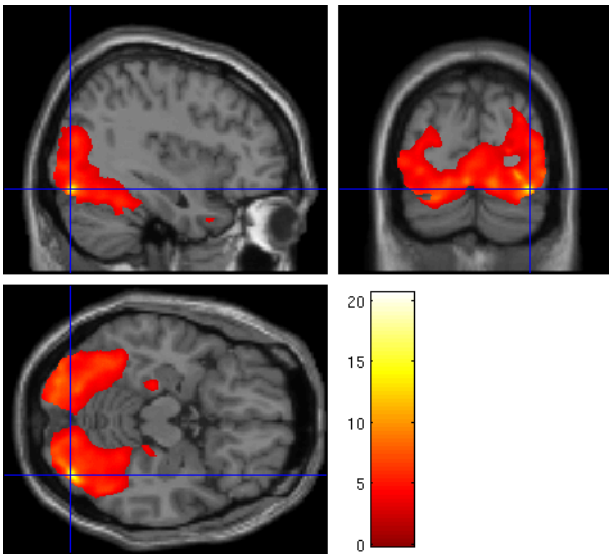
Figure 1: Psychophysiological Interaction (PPI) whole brain result images for the group-level negative emotion contrast, left FFA as PPI source VOI. Global maximum and local maxima located on the left hemisphere (uncorrected $p < .01$, cluster threshold 10).



(a) Local maximum at 25, -92, -2.

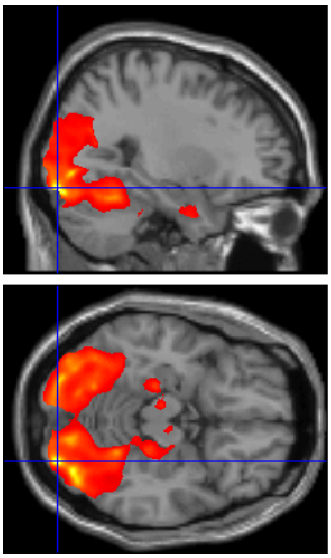


(b) Local maximum at 29, -84, -7.

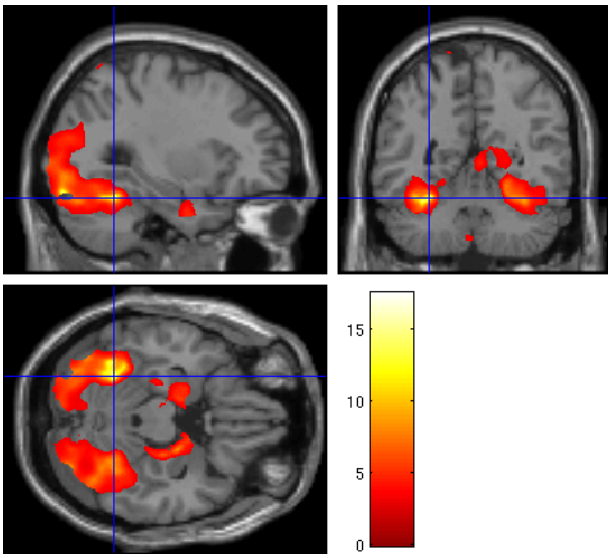


(c) Local maximum at 38, -81, -16.

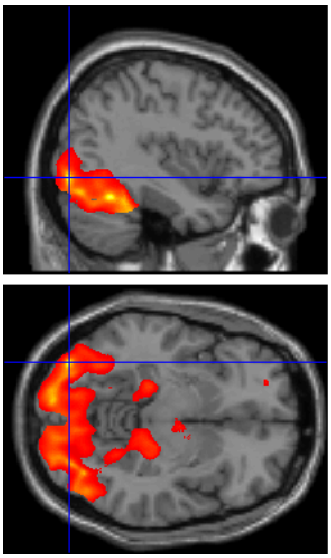
Figure 2: Psychophysiological Interaction (PPI) whole brain result images for the group-level negative emotion contrast, left FFA as PPI source VOI. Local maxima located on the right hemisphere (uncorrected $p < .01$, cluster threshold 10).



(a) Global maximum at 29, -90, -15.



(b) Local maximum at -29, -52, -22.



(c) Local maximum at -38, -82, -8.

Figure 3: Psychophysiological Interaction (PPI) whole brain result images for the group-level negative emotion contrast, right FFA as PPI source VOI. Global and local maxima (uncorrected $p < .01$, cluster threshold 10).

Table 4: Psychophysiological Interaction (PPI) Whole Brain Results for the Negative Emotion Contrast

source region	set p	set c	cluster p_{FWE}	cluster p_{FDR}	k_E	cluster p_{unc}	peak p_{FWE}	peak p_{FDR}	peak T	peak Z	peak p_{unc}	X	Y	Z	peak region
L OFA 10mm (n = 5)	NSTC														
R OFA 10mm (n = 8)	NSTC														
L FFA 10mm (n = 12)	<.001	4	<.001	<.001	156	<.001	<.001	.044	20.59	6.26	<.001	-7	-98	7	L cuneus
			<.001	<.001	555	<.001	<.001	.044	20.53	6.25	<.001	25	-92	-2	R MOG
							.021	.517	12.34	5.35	<.001	29	-84	-7	R IOG
			<.001	<.001	148	<.001	.002	.122	16.45	5.87	<.001	38	-81	-16	R BA18/MOG
			<.001	<.001	302	<.001	.005	.181	15.16	5.73	<.001	-23	-91	-10	L LG
							.024	.517	12.19	5.33	<.001	-16	-95	-12	L LG
R FFA 10mm (n = 10)	<.001	3	.002	.129	7	.043	.021	.963	17.50	5.55	<.001	29	-90	-15	R IOG
			.013	.383	2	.256	.044	.963	15.41	5.35	<.001	-29	-52	-22	L culmen/cerebellum
			.021	.423	1	.423	.048	.963	15.14	5.32	<.001	-38	-82	-8	L BA19/IOG

Note. set c = expected number of clusters in set; FWE = family-wise error; FDR = false discovery rate; unc = uncorrected; kE = expected number of voxels in cluster; L = left; R = right; NSTC = no suprathreshold clusters; MOG = middle occipital gyrus; BA = Brodmann area; LG = lingual gyrus; IOG = inferior occipital gyrus. Peak p_{FWE}<0.05, extent threshold in voxels = 0. All coordinates are in Montreal Neurological Institute (MNI) space.

Table 5: Psychophysiological Interaction (PPI) Volume of Interest (VOI) Results for the Negative Emotion Contrast Using Left Occipital Face Area (OFA) as Source Region

target region	set p	set c	cluster p_{FWE}	cluster p_{FDR}	k_E	cluster p_{unc}	peak p_{FWE}	peak p_{FDR}	peak T	peak Z	peak p_{unc}	X	Y	Z
R OFA 10mm	.581	1	.101	.122	2977	.122	.194	.611	8.14	3.23	.001	39	-78	-15
							.311	.611	5.17	2.71	.003	31	-89	-13
							.323	.611	4.96	2.67	.004	31	-83	-7
							.354	.611	4.49	2.55	.005	31	-87	-9
							.376	.611	4.20	2.47	.007	33	-77	-7
							.386	.611	4.07	2.43	.008	29	-83	-18
							.413	.611	3.75	2.33	.010	33	-90	-17
L FFA 10mm	.581	1	.084	.101	3382	.101	.152	.599	10.17	3.47	<.001	-40	-58	-29
							.174	.599	8.99	3.34	<.001	-28	-59	-22
							.177	.599	8.83	3.32	<.001	-28	-52	-26
							.200	.599	7.89	3.20	.001	-33	-57	-30
							.263	.635	6.11	2.91	.002	-30	-54	-29
							.271	.635	5.93	2.88	.002	-34	-54	-25
							.329	.712	4.87	2.64	.004	-36	-51	-20
							.384	.776	4.09	2.43	.007	-39	-47	-20
							.412	.776	3.76	2.33	.010	-37	-45	-24
							.527	.915	2.62	1.90	.029	-41	-61	-17
							.549	.915	2.42	1.80	.036	-36	-59	-13
R FFA 10mm	.581	1	.108	.132	2813	.132	.339	.811	4.72	2.61	.005	35	-50	-29
							.343	.811	4.65	2.59	.005	34	-54	-27
							.356	.811	4.46	2.54	.006	41	-58	-15
							.363	.811	4.37	2.51	.006	44	-60	-25
							.394	.811	3.97	2.40	.008	43	-60	-19
							.404	.811	3.85	2.36	.009	39	-54	-15
							.420	.811	3.67	2.30	.011	33	-48	-25
							.462	.811	3.23	2.15	.016	39	-50	-18
							.487	.811	2.99	2.05	.020	47	-56	-15

Note. set c = expected number of clusters in set; FWE = family-wise error; FDR = false discovery rate; unc = uncorrected; kE = expected number of voxels in cluster; L = left; R = right. n = 5. All coordinates are in Montreal Neurological Institute (MNI) space.

Table 6: Psychophysiological Interaction (PPI) Volume of Interest (VOI) Results for the Negative Emotion Contrast Using Right Occipital Face Area (OFA) as Source Region

target region	set p	set c	cluster p_{FWE}	cluster p_{FDR}	k_E	cluster p_{unc}	peak p_{FWE}	peak p_{FDR}	peak T	peak Z	peak p_{unc}	X	Y	Z
L OFA 10mm	.571	1	.134	.170	2334	.170	.005	.038	11.72	4.48	<.001	-36	-86	-15
							.020	.053	8.02	3.92	<.001	-31	-88	-15
							.028	.053	7.27	3.76	<.001	-34	-83	-12
							.032	.053	7.04	3.71	<.001	-29	-76	-27
							.116	.170	4.73	3.07	.001	-27	-86	-23
							.280	.388	3.31	2.49	.006	-38	-74	-23
L FFA 10mm	.571	1	.062	.076	4092	.076	.005	.095	11.44	4.45	<.001	-29	-52	-24
							.040	.131	6.58	3.61	<.001	-37	-51	-28
							.049	.131	6.20	3.51	<.001	-33	-55	-30
							.054	.131	6.03	3.47	<.001	-40	-56	-19
							.062	.131	5.80	3.40	<.001	-38	-52	-19
							.065	.131	5.71	3.38	<.001	-42	-58	-27
							.079	.133	5.38	3.28	.001	-40	-48	-19
							.088	.133	5.19	3.22	.001	-41	-55	-23
							.141	.180	4.41	2.96	.002	-34	-59	-13
R FFA 10mm	.571	1	.079	.097	3527	.097	.002	.020	14.93	4.82	<.001	35	-55	-26
							.021	.104	7.92	3.90	<.001	33	-48	-23
							.067	.280	5.64	3.36	<.001	38	-47	-21
							.158	.574	4.24	2.89	.002	44	-47	-21
							.237	.634	3.58	2.62	.004	44	-60	-24
							.348	.634	2.94	2.30	.011	38	-51	-14
							.369	.634	2.83	2.24	.013	42	-52	-16
							.379	.634	2.79	2.21	.013	45	-55	-14
							.392	.634	2.72	2.18	.015	39	-56	-15

Note. set c = expected number of clusters in set; FWE = family-wise error; FDR = false discovery rate; unc = uncorrected; kE = expected number of voxels in cluster; L = left; R = right. n = 8. All coordinates are in Montreal Neurological Institute (MNI) space.

Table 7: Psychophysiological Interaction (PPI) Volume of Interest (VOI) Results for the Negative Emotion Contrast Using Left Fusiform Face Area (FFA) as Source Region

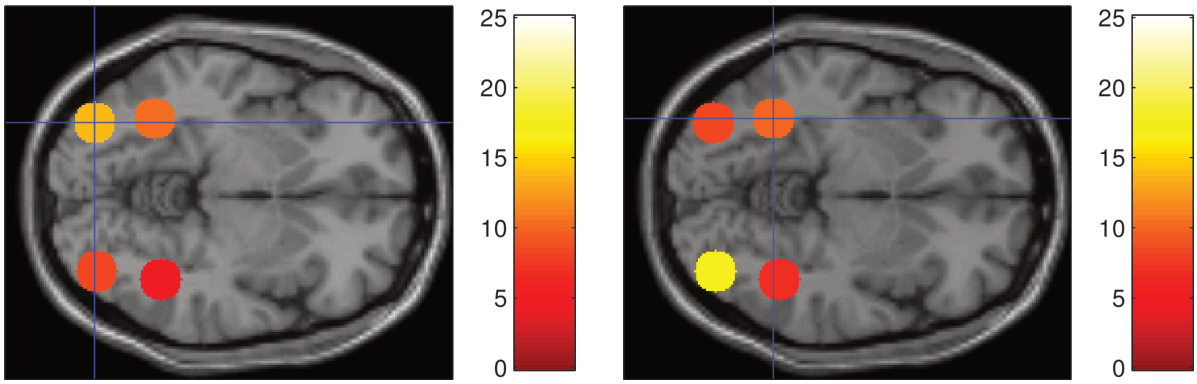
target region	set p	set c	cluster p_{FWE}	cluster p_{FDR}	k_E	cluster p_{unc}	peak p_{FWE}	peak p_{FDR}	peak T	peak Z	peak p_{unc}	X	Y	Z
L OFA 10mm	.575	1	.158	.201	1968	.201	.001	.004	8.15	4.55	<.001	-25	-81	-22
							.002	.004	8.05	4.52	<.001	-27	-88	-17
							.002	.004	7.85	4.47	<.001	-35	-88	-16
							.002	.004	7.82	4.46	<.001	-34	-74	-21
							.003	.005	7.30	4.32	<.001	-32	-79	-22
							.009	.012	6.14	3.97	<.001	-40	-84	-16
							.016	.019	5.60	3.78	<.001	-41	-78	-17
R OFA 10mm	.575	1	.093	.115	3086	.115	<.001	<.001	16.45	5.87	<.001	38	-81	-16
							<.001	<.001	11.07	5.15	<.001	31	-83	-8
							<.001	<.001	10.99	5.13	<.001	30	-87	-11
							.001	.002	8.14	4.54	<.001	45	-79	-8
							.018	.021	5.51	3.74	<.001	38	-82	-4
R FFA 10mm	.575	1	.073	.088	3661	.088	.005	.020	6.70	4.15	<.001	33	-51	-23
							.008	.020	6.34	4.03	<.001	47	-56	-16
							.010	.020	6.03	3.93	<.001	44	-48	-20
							.011	.020	5.93	3.90	<.001	34	-57	-22
							.024	.032	5.21	3.63	<.001	42	-60	-19
							.037	.044	4.81	3.46	<.001	43	-42	-25

Note. set c = expected number of clusters in set; FWE = family-wise error; FDR = false discovery rate; unc = uncorrected; kE = expected number of voxels in cluster; L = left; R = right. n = 12. All coordinates are in Montreal Neurological Institute (MNI) space.

Table 8: Psychophysiological Interaction (PPI) Volume of Interest (VOI) Results for the Negative Emotion Contrast Using Right Fusiform Face Area (FFA) as Source Region

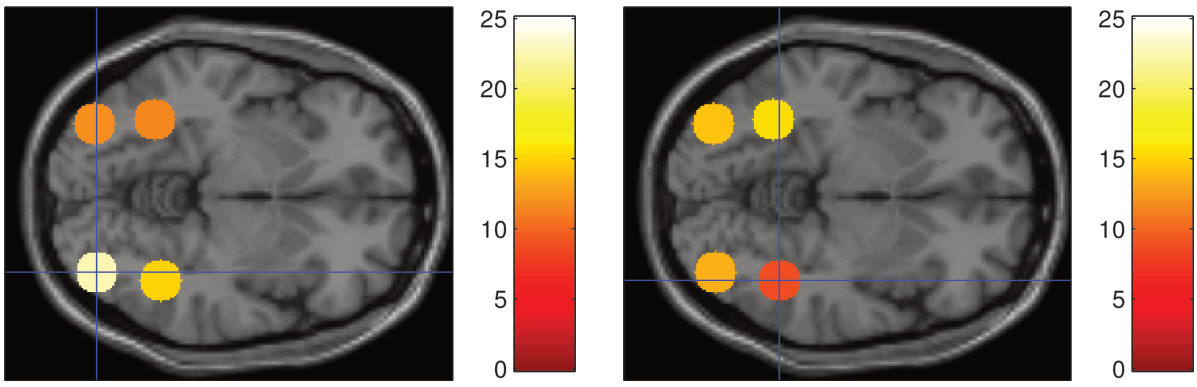
target region	set p	set c	cluster p_{FWE}	cluster p_{FDR}	k_E	cluster p_{unc}	peak p_{FWE}	peak p_{FDR}	peak T	peak Z	peak p_{unc}	X	Y	Z
L OFA 10mm	.597	1	.132	.156	2220	.156	<.001	.002	13.91	5.18	<.001	-29	-86	-18
							.002	.007	10.09	4.65	<.001	-36	-77	-17
							.003	.007	9.34	4.52	<.001	-37	-82	-13
							.006	.010	7.97	4.24	<.001	-31	-75	-23
							.012	.015	7.01	4.00	<.001	-28	-81	-21
							.034	.039	5.60	3.59	<.001	-28	-85	-23
R OFA 10mm	.597	1	.079	.090	3267	.090	<.001	.002	13.46	5.13	<.001	37	-75	-11
							<.001	.002	13.21	5.10	<.001	36	-80	-15
							.001	.002	12.11	4.96	<.001	30	-87	-17
							.004	.005	8.66	4.38	<.001	31	-80	-8
							.221	.275	3.40	2.66	.004	38	-82	-4
L FFA 10mm	.597	1	.052	.059	4169	.059	<.001	.001	15.41	5.35	<.001	-29	-52	-22
							<.001	.001	13.90	5.18	<.001	-33	-51	-24
							<.001	.001	13.89	5.18	<.001	-38	-55	-21
							<.001	.001	12.97	5.07	<.001	-32	-47	-21
							<.001	.001	12.86	5.06	<.001	-31	-56	-22
							<.001	.001	12.65	5.03	<.001	-35	-46	-24
							.008	.010	7.58	4.14	<.001	-35	-63	-24
							.021	.025	6.23	3.79	<.001	-39	-61	-15
							.039	.044	5.44	3.53	<.001	-34	-59	-13

Note. set c = expected number of clusters in set; FWE = family-wise error; FDR = false discovery rate; unc = uncorrected; kE = expected number of voxels in cluster; L = left; R = right. n = 10. All coordinates are in Montreal Neurological Institute (MNI) space.



(a) Left OFA as PPI source VOI.

(b) Left FFA as PPI source VOI.



(c) Right OFA as PPI source VOI.

(d) Right FFA as PPI source VOI.

Figure 4: Visualization of group-level PPI VOI analyses. Each blob's z-coordinate has been fixed to -5 for visualization purposes. Colors represent the T value of the top voxel of the VOI. Crosshead marks the PPI source VOI. Uncorrected $p < .05$, cluster threshold 0. PPI = psychophysiological interaction; VOI = volume of interest; OFA = occipital face area; FFA = fusiform face area.

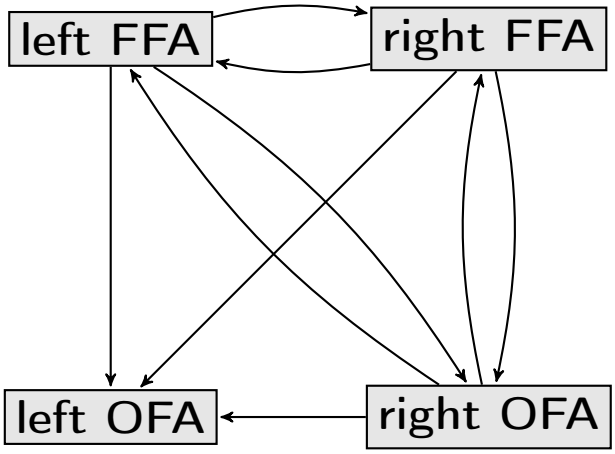


Figure 5: Demonstrated bilateral OFA-FFA network during processing of negative emotion, based on group-level PPI VOI analyses. Arrows point from PPI source VOIs to target VOIs. FFA = fusiform face area; OFA = occipital face area; PPI = psychophysiological interaction; VOI = volume of interest.

4 Discussion

4.1 Whole Brain Analyses of Psychophysiological Interaction (PPI)

This study showed that activations of the left FFA for negative emotion influenced several regions in the extended visual network: left cuneus, right MOG, right IOG, and left LG. Clearly this reflects the essential role of the FFA in visual processing. For each PPI of these regions there are three possible mutually non-exclusive explanations: direct influence from the left FFA, indirect influence from the left FFA (through some other region), or a common input for both left FFA and the PPI region from a region that itself is sensitive to the emotional content of the stimuli. The results indicate the importance of the MOG and the LG regarding neural processing of visual emotional content. PPI does not enable inferences on the direction of information flow. The effect may be caused by a direct influence, an indirect influence (ie. mediated through other regions) or there may be a region that provides common input for the source region and the target voxel (K. J. Friston et al., 1997).

Activations of the right FFA for negative emotion influenced the left and right IOG and the left culmen, a cerebellar region. A culmen infarct is reported to cause body backpulsion (Ikeda et al., 2009) and therefore the culmen seems to contribute towards maintaining the position and posture of the body.

4.2 Volume of Interest (VOI) Analyses of Psychophysiological Interaction (PPI)

VOI analyses demonstrated the strong connectivity in the network consisting of the right OFA and left and right FFAs. Each of these regions influences all other regions and the left OFA. The PPIs of the left OFA activations for negative emotion contrast were not statistically significant (all p_{FWE} were $> .05$) but presumably the left OFA is also part of the network. This difference between the left and the right OFA is in line with the right-hemisphere dominance of the OFA (Minnebusch et al., 2009; Rossion, Caldara, et al., 2003).

It should be noted that PPI is not a correlation: in the PPI analysis the BOLD response of each voxel is modeled with the PPI interaction term, the eigenvariate of the BOLD signal of the source VOI, and the main effect of emotion. However, standard PPI analysis can not

be used to make inferences about the direction of information flow or causality (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012).

Strengths of the present study include well-established VOI coordinates from an earlier study (Rossion, Caldara, et al., 2003) and the passive viewing task, as an emotion labeling task has been shown to reduce neural activity in some regions (S. F. Taylor, Phan, Decker, & Liberzon, 2003). Other strength of the present study is the use of IAPS, a well-established and standardized image set for visual emotion research.

Weaknesses of the present study include the relatively low number of subjects, and the possible bias caused by VOI-wise exclusion of certain contrasts from subjects with statistically non-significant activations. PPI does not enable inferences on the directions of information flow between brain regions (O'Reilly et al., 2012).

The results of the present study indicate that negative emotional content enhances effective connectivity in the bilateral OFA-FFA network. If these regions are considered to be domain-general regions specialized in identifying the specific identity of the stimuli within a category (Haist et al., 2010), the results show that negative emotional content enhances such activity in the network as measured by PPIs between the regions of the network. Alternatively, if the OFA and the FFA are assumed to be face-specific identification regions (Brassen et al., 2010; Fairhall & Ishai, 2007; Rossion, Schiltz, & Crommelinck, 2003), the conclusion would be that negative emotional content enhances person identification activity in these regions as indicated by PPIs between the regions of the network. In both cases the top-down modulation from hierarchically higher regions to the OFA and the FFA would impose synchronized activity within the bilateral OFA-FFA network (see Carretié et al., 2005).

Using DCM instead of PPI would enable inferences on the flow of the information with higher certainty. In this study, DCM did not produce any meaningful results for our data because of the use of the interleaved EPI sequence, which is suboptimal for DCM (Stephan et al., 2010).

4.3 Conclusions

This study demonstrated the effective connectivity of the bilateral OFA-FFA network using IAPS stimuli and PPI. This study represents basic research of visual neural network and as such contributes to the expanding knowledge of the functioning of the visual neural network.

The results implicate that negative emotional content enhances the effective connectivity between the OFAs and the FFAs. This is also true with complex visual stimuli with human content.

Future studies should expand the knowledge of the visual neural network using emotional scene images. In particular, using non-interlaced EPI sequence would permit the analysis of the data with DCM to understand the causal effect of each region of the visual neural network better. Combined fMRI and EEG studies or combined fMRI and magnetoencephalography (MEG) studies (see Northoff et al., 2000) would permit combining the benefits of higher spatial resolution of fMRI and superior temporal resolution of EEG/MEG, which would be beneficial in trying to deduce the neural codings of the visual neural network.

Future studies could replicate the PPI results of the present study using DCM. However, the development of more advanced preprocessing and analytical methods (particularly slice timing) may change the situation in the future.

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